European Psychiatry 30 (2015) 89–93

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Links between sleep and body mass index in bipolar disorders: An exploratory study☆

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ARTICLE INFO

Article history:
Received 15 January 2014
Received in revised form 23 March 2014
Accepted 19 April 2014
Available online 5 June 2014

Keywords:
Bipolar disorder
Sleep efficiency
Actigraphy
Circadian
BMI
Obesity

ABSTRACT

Study objectives: Obesity and excess bodyweight are highly prevalent in individuals with bipolar disorders (BD) and are associated with adverse consequences. Multiple factors may explain increased bodyweight in BD including side effects of psychotropic medications, and reduced physical activity. Research in the general population demonstrates that sleep disturbances may also contribute to metabolic burden. We present a cross-sectional study of the associations between body mass index (BMI) and sleep parameters in patients with BD as compared with healthy controls (HC).
Methods: Twenty-six French outpatients with remitted BD and 29 HC with a similar BMI completed a 21-day study of sleep parameters using objective (actigraphy) and subjective (PSQI: Pittsburgh Sleep Quality Index) assessments.
Results: In BD cases, but not in HC, higher BMI was significantly correlated with lower sleep efficiency ($P = 0.009$) and with several other sleep parameters: shorter total sleep time ($P = 0.01$), longer sleep onset latency ($P = 0.05$), higher fragmentation index ($P = 0.008$), higher inter-day variability ($P = 0.05$) and higher PSQI total score ($P = 0.004$).
Conclusions: The findings suggest a link between a high BMI and several sleep disturbances in BD, including lower sleep efficiency. Physiological mechanisms in BD cases may include an exaggeration of phenomena observed in non-clinical populations. However, larger scale studies are required to clarify the links between metabolic and sleep-wake cycle disturbances in BD.

1. Introduction

Bipolar disorders (BD), defined as recurrences of major depressive and (hypo)manic episodes, affect at least 1% of the population [22]. Inter-episode residual depressive symptoms, sleep disturbances and somatic comorbidities, particularly obesity or metabolic syndrome, contribute to poor quality of life, functional impairment and clinical outcomes [18].

Whilst sleep disturbance is one of the diagnostic criteria for both depressive and manic episodes, it is often evidence during periods of remission as well. Persistent sleep problems and insomnia are frequent euthymic BD cases, with polysomnography and actigraphy studies showing disturbances in sleep continuity and duration [12]. Furthermore, insomnia is a robust prodromal symptom of BD relapse [15].

Obesity is frequent among those who suffer from severe mental disorders [19]. BD cases are four times more likely than individuals with no psychiatric condition to be obese or overweight [9], and

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http://dx.doi.org/10.1016/j.eurpsy.2014.04.006
0924-9338/

their life expectancy is reduced by about 10 years due to cardiovascular and metabolic diseases [30]. High body mass index (BMI) impacts negatively on clinical and functional outcomes in BD. Indeed bipolar patients with obesity reported greater impairment in quality of life than non-psychiatric individuals with obesity and than non-obese psychiatric patients [17]. Furthermore, high BMI negatively influences treatment response to mood stabilizers such as lithium and valproate, and the likelihood of remission [16]. In BD, the pathophysiology of weight gain is incompletely understood. Genetic susceptibility, recurrent depressions, low activity levels, poor dietary habits, poor medical care, and side effects of antipsychotics/mood-stabilizers medication may all play a part [21].

Links between sleep disturbances and weight gain are already well documented in the general population, with an association reported between shorter sleep duration and risk of being overweight [26]. More specifically among remitted patients with BD, an association between evening chronotype and higher percentage of body fat composition had been suggested [33] and shorter sleep duration was associated with low HDL cholesterol [34].

To our knowledge, there are no published data on any associations between BMI and sleep parameters in BD cases who are in remission. Our first hypothesis was that BMI would be inversely related to sleep efficiency assessed by actigraphy in BD cases as compared with healthy controls (HC). In addition, we undertook subsidiary, exploratory analyses, to see if similar relationships existed between BMI and other sleep parameters in both cases and controls.

2. Methods

2.1. Sample

With ethical approval, written informed consent was obtained from 26 BD outpatients who were currently in remission and 29 HC. The BD cases were recruited from the Paris Est University-affiliated psychiatric department whilst the HC were recruited from the general population via advertisements posted at blood donor centres between January and August 2012.

As the study focused on ecological sleep-wake patterns, primary exclusion criteria for both groups related to confounders of sleep-wake cycle, including: shift work, recent trans-meridian travel (with a $>$ 3-hour time difference), pregnancy, child birth or recent bereavement occurring within two months before the study.

Included cases met DSM-IV criteria for BD (diagnosed using the Diagnostic Interview for Genetic Studies [DIGS]) [25], whilst HC had no personal history of a DSM-IV mental disorder (assessed using the DIGS), and no first-degree relative with a mood or psychotic disorder, or suicide attempts (assessed with the Family Interview for Genetic Studies: FIGS) [20]. Mood symptoms were measured in both groups using the Young Mania Rating Scale (YMRS) [38], and the Montgomery Asberg Depression Rating Scale (MADRS) [24].

For BD cases, remission was defined as the absence of a current or recent (within 3 months) major mood episode (according to the DIGS mood section), plus a score $<$ 8 on both the MADRS and the YMRS. Cases were also excluded if in the 3 months prior to interview they had been hospitalized for a major mood episode (DSM-IV criteria), and/or had any change in psychiatric medications.

2.2. Sleep and BMI assessment

2.2.1. Actigraphy measure of sleep

Actigraphy allows the prospective and objective monitoring of sleep (inactivity) and activity patterns, and can capture the variability in sleep-wake patterns over several consecutive days. For the purposes of this study, we selected sleep efficiency as our primary as it is widely reported in sleep and circadian studies and in those with physical and mental disorders; sleep efficiency and BMI are known to be correlated in healthy populations [23]; also, it is a composite measure that takes into account time in bed and total sleep time, all of which can be measured objectively using an actiwatch.

All study participants were asked to wear an actiwatch (AW-7 CamNtech®) continuously on the non-dominant wrist for 21 consecutive days. An actiwatch is a device that contains an accelerometer and detects, scores, and stores information about the intensity and timing of wrist movements over consecutive 24-hour intervals. Participants were instructed to press the event-marker when they went to bed to sleep and when they got out of bed to start the day (and concurrently to complete a sleep diary). Data were sampled in one-minute epochs and analyzed with the sleep detection algorithm provided by Actiwatch software (Actiwatch Activity & Sleep Analysis Ltd CamNtech® 7.28). The following sleep scoring procedure was used: (i) information provided by the event-marker was given priority, (ii) if participants forgot to press the event-marker, missing information about bed- and/or rise-times was retrieved from the sleep diary, (iii) visual inspection was used to correct any inconsistencies between the times provided by the event-marker, the diary and/or the recorded signal [5]. The definitions of the actigraphy parameters of interest are summarized in Table 1.

2.2.2. Sleep questionnaires

Participants completed the French version of the Pittsburgh Sleep Quality Index (PSQI) [2] and the French version of the Berlin Questionnaire [31]. The PSQI is a 19-item self-rated questionnaire that measures subjective sleep quality. A total score $>$ 5 is regarded as indicating clinical significant levels of sleep disturbances. As discrepancies between objective and subjective measure of sleep are common in BD [13], we regarded the examination of the associations between BMI and PSQI total score as secondary analysis. The Berlin Questionnaire is a validated assessment of an individual's risk of Obstructive Sleep Apnea (OSA) [31]. Since a substantial proportion of obese individual and patients with BD who are overweight are known to present with OSA [35], we included this as a putative moderating variable in our analysis. The Berlin Questionnaire identifies three risk categories for OSA and individuals can be classified into high risk (if they have positive scores for $\geq$ 2 categories) or low risk (if they have a positive score $\leq$ 1 category).

Table 1
Definitions of the actigraphy parameters.

Actigraphy parameters	Definitions
Sleep efficiency	Ratio of time spent asleep (total sleep time) to the amount of time spent in bed
Total sleep time	Time period from sleep onset to wake up time
Sleep onset latency	Time period from lights out/bedtime to sleep onset
Wake after sleep onset (WASO)	Total amount of time awake excluding sleep onset latency
Intra-day variability	Variation in activity levels within one day
Fragmentation index	Ratio of the number of phases of 1-minute immobility to the total number of immobility phases of all duration multiplied by 100

2.2.3. BMI measure

BMI was calculated at inclusion for every participant using data from a direct measure of the persons' height and weight (the same weighing scale was used for all participants).

2.2.4. Psychotropic medications

Data on prescribed psychotropic treatments were recorded for BD cases (none of the HC was being prescribed these medications). This was considered relevant as it is known for example that lithium and valproate lengthen the circadian period [7,37] and reduce melatonin light sensitivity [10,11]. Similarly, benzodiazepines and antipsychotics are known to have sedative effects and could act as confounders in this study.

2.3. Statistical analysis

Data analysis was conducted using JMP® Pro 9.0.0 (SAS Institute®). Non-parametric tests (Mann-Whitney) were used to compare cases and controls on continuous demographic and clinical variables; Fisher's exact tests were used for categorical variables, and Spearman's tests were used to examine bivariate correlations. To test the impact of psychotropic treatments on the primary outcome measures, we divided the BD group into patients who received at least one treatment with sedative effects (atypical antipsychotics, typical antipsychotics, benzodiazepines) and patients who did not. Partial correlations were used to control for putative confounders (OSA risk, exposure to sedative medications). The primary parameters of interests were sleep efficiency and BMI. Secondary measures were: sleep onset latency, total sleep time, wake after sleep onset, fragmentation index, intra-day variability assessed by actigraphy and PSQI total score.

3. Results

3.1. BD cases: demographics and clinical characteristics

Nine of the 26 BD cases were female with a mean age of about 54 years. There were 16 cases with type I BD, eight with type II BD and two with BD NOS; the mean age of onset of BD was 27 years old (SD = 11), with a mean duration of illness of about 27 years (SD = 13). The mean number of prior BD episodes was six (SD = 4), but in eight cases, the total number could not be estimated accurately. Likewise, the mean number of hospitalisations was four (SD = 3) for 23 cases with prior admissions, whilst three cases had never been hospitalized. Eleven cases had at least one comorbid mental disorder (the most frequent being: panic disorder $n = 6$; social phobia $n = 4$; and alcohol abuse $n = 4$). Half the cases had a life-time history of suicidal behaviours, 28% of rapid cycling disorder and 50% of psychotic symptoms.

Twenty-five BD cases were being prescribed at least one psychotropic medication (lithium = 12; anti-convulsants = 15; atypical antipsychotics = 7; typical antipsychotics = 4; benzodiazepines = 5; antidepressants = 5); nine individuals were prescribed ≥ 2 mood stabilizers. Twelve patients were receiving at least one treatment with sedative effects (atypical antipsychotics, typical antipsychotics, or benzodiazepines).

3.2. Comparison of BD cases and HC

Table 2 shows that mean BMI score and risk for OSA did not differ between BD cases and HC, and that the groups were comparable for mean current age and gender distribution. Although all BD cases met criteria for remission, the BD group reported a significantly higher level of depressive symptoms compared to HC, but levels of manic symptom did not differ.

Table 2
Demographic and clinical characteristics of cases and controls.

Variables	Bipolar group ($n = 26$) Mean (SD) Median	Control group ($n = 29$) Mean (SD) Median	Fisher or Mann-Whitney test[a]
Age	53.50 (11.49)	54.10 (9.11)	U = 711.5
	55.5	55	$P = 0.79$
Gender males: females (n)	9:17	16:13	$P = 0.18$
BMI range[a]	19.5–39.4	19.1–37.0	
	26.74 (1.12)	26.64 (0.77)	U = 703.5
	25.83	26.57	$P = 0.69$
Risk of OSA: low/high	20/6	27/2	$P = 0.13$
MADRS score	1.85 (2.80)	0.48 (1.35)	U = 845.5
	1	0	$P = 0.02$
YMRS score	0.65 (1.38)	0.14 (0.44)	U = 782
	0	0	$P = 0.16$
PSQI total score	7.38 (3.5)	4.11 (2.13)	U = 915.5
	7	4	$P = 0.0005$

Since most variables did not fit a normal distribution, medians are also provided. OSA: Obstructive Apnea Risk; MADRS: Mongomery Asberg Depression Rating Scale; YMRS: Young Manic Rating Scale; PSQI: Pittsburgh Sleep Quality Index.
[a] Six bipolar patients (23%) and 6 controls (21%) met criteria for obesity.

Compared with HC, BD cases reported significantly poorer subjective sleep quality on the PSQI ($P = 0.0005$).

3.3. Correlations between BMI and sleep parameters

For primary outcome measures, we observed that BMI was highly correlated with sleep efficiency assessed by actigraphy (rho = −0.50; $P = 0.009$) in cases with BD only. Exploratory analysis suggested that BMI was also correlated with total sleep time ($P = 0.01$), sleep onset latency ($P = 0.03$), fragmentation index ($P = 0.008$) and intra-day variability ($P = 0.04$) amongst cases, but not HC (Table 3). Subjective sleep quality (PSQI total score) was significantly correlated with BMI in BD cases only ($P = 0.004$).

3.4. Partial correlations between sleep efficiency and BMI, after controlling for risk of OSA and sedative treatments

Partial correlations showed that BMI and sleep efficiency were correlated (rho = −0.44; $P = 0.03$). However BMI was neither correlated with the risk of OSA (rho = −0.08; $P = 0.70$) nor with the use of sedative treatments (rho = 0.31; $P = 0.14$).

Table 3
Spearman's correlation coefficients of body mass index (BMI) and sleep parameters.

Sleep parameters	Bipolar group ($n = 26$) BMI	Control group ($n = 29$) BMI
Primary outcome measures		
Sleep efficiency	Rho = −0.50	Rho = −0.04
	$P = 0.009$	$P = 0.83$
Secondary outcome measures		
Total sleep time	Rho = −0.49	Rho = −0.35
	$P = 0.01$	$P = 0.06$
Sleep onset latency	Rho = 0.43	Rho = −0.07
	$P = 0.03$	$P = 0.72$
Wake after sleep onset (WASO)	Rho = 0.25	Rho = −0.15
	$P = 0.22$	$P = 0.44$
Intra-day variability	Rho = 0.41	Rho = −0.08
	$P = 0.04$	$P = 0.67$
Fragmentation index	Rho = 0.50	Rho = −0.05
	$P = 0.008$	$P = 0.79$
PSQI total score	Rho = 0.52	Rho = −0.06
	$P = 0.004$	$P = 0.77$

4. Discussion

To our knowledge, this is the first study that highlights concurrent associations between BMI and sleep efficiency in BD cases in remission. In cases and controls with comparable BMI and comparable risk of OSA, we identified significant correlations between sleep parameters measured by actigraphy, specifically sleep efficiency and BMI in the BD group but not in HC. Also, in BD cases, a higher BMI score was significantly correlated with alterations in subjective sleep quality.

The associations between sleep disturbance and BMI could represent an exacerbation of the patterns observed in obese individuals in the general population, or could be an epiphenomena, linked to the post-illness onset/treatment phase of BD (e.g. cumulative effects of risk factors for obesity such as side effects of medication or poor dietary habits, etc). However, some of the changes in sleep parameters have been identified as putative trait markers of BD, suggesting the possibility of a shared susceptibility to BD and metabolic disturbances that are manifested as obesity/weight gain. For example, research has demonstrated the important role played by core clock genes in both glucose homeostasis and in mood regulation [14].

The influence of weight on sleep can be mediated by peptides like leptin, orexin and/or ghrelin that are known to play a role in the regulation of food-intake and the sleep-wake cycle [8]. For example, ghrelin, a hormone produced by the stomach, is involved in body weight regulation and is associated with sleep duration; a recent study in rats also suggested an influence of ghrelin on amygdala neurons, which is part of the emotional brain [32]. Orexin is a neurotransmitter that regulates wakefulness and food intake and has been linked to emotion regulation in patients with narcolepsy [3]. Likewise, leptin, which is produced by adipocytes, regulates appetite and modulates sleep duration. Increased levels of leptin have been described previously in overweight patients with BD as compared with overweight controls [1]. Given the links we have shown between BMI and sleep parameters, further studies of these peptides, metabolomics and sleep patterns in BD are clearly warranted.

The relationship between bodyweight and sleep-wake cycle can also be hypothesized to be a manifestation of the association of the former with OSA. Even though our exploratory study did not demonstrate that OSA risk moderated the association between BMI and sleep efficiency among the BD cases, it was noteworthy that over half of the obese BD cases (54%) were in the high risk category for OSA [35].

Sleep disturbances can also have an impact on weight. Our findings are consistent with Harvey's model of BD, that integrates genetic susceptibility, sleep and circadian functioning, neurotransmitter output and mood dysregulation [12]. We can hypothesize that genetic factors predispose to sleep disturbances and circadian dysregulations leading to changes in the dopamine and serotonin circuitry in individuals who develop BD. As such, these disturbances are likely to have effects, not only on mood regulation, but also on weight gain [36]. Other mechanisms worthy of further research include the links between sleep disturbances, inflammatory markers and BD [18,27], as it is logical to propose a trilateral relation between sleep, metabolic disturbances and inflammatory dysfunction [28,29]. Taken together all these avenues of research may shed light on the co-occurrence and on various patho-physiological processes underlying weight gain in BD.

This pilot study has several limitations. First, our study may have insufficient statistical power to detect any associations between BMI and sleep parameters in the HC group. Indeed, we observed a trend towards significance between BMI and total sleep time ($P = 0.06$) in HC and previous research in a larger HC sample has identified a link between short sleep duration and BMI [26]. The lack of association between BMI and sleep parameters in HC can also be explained by the lack of variance of sleep parameters distribution. Larger control groups or matching of cases and controls on specified baseline variables may be needed in future to examine these issues further. Also, as the BD cases were recruited after illness onset and were receiving psychotropic treatments that can impact on both sleep and BMI, further studies will also need to consider methodologies that can control or minimize the impact of the confounding effects of medication. In this study, we grouped cases according to the use of medications with sedative effects and studied their impact on our main outcome measure. However, this approach assumed that all antipsychotics and benzodiazepines have similar effects, which is too simplistic. Furthermore, we did not differentiate medications used for BD that influence body weight from those that influence sleep or from those that may influence both, again these issues are worthy of greater consideration in future studies of larger samples [4,6]. Our design was cross-sectional, and a prospective study would help confirm the association between BMI and sleep efficiency in BD cases and also establish if these associations change over time and with illness phase. Finally, the risk of OSA was measured by questionnaire, not an objective measure, like PSG. The latter of course offer a better assessment of the risk of OSA and the risk for other sleep disorders that need to be taken into account in BD studies.

5. Conclusion

We propose that simultaneous evaluation of sleep and body weight in BD cases, even during periods of remission, is an important first step in initiating more systematic approaches to these linked problems. Further studies will help to clarify the nature and underlying causes of the associations between sleep disturbances and increased BMI among cases with BD.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

We thank all the study participants and our colleagues at Paris-Créteil for their participation in the clinical assessment (E. Abadie, A. Raust and B. Cochet). We are also grateful to colleagues at the Clinical Investigation Centre (O. Montagne and P. Le Corvoisier).

Funding

This work was supported by Inserm (Institut National de la Santé et de la Recherche Médicale), AP–HP (Assistance Publique des Hôpitaux de Paris) and the Fondamental foundation (RTRS Santé Mentale).

FondaMental Foundation is supported in part by the Investissements d'Avenir, program managed by the ANR under reference ANR-11-IDEX-0004-02.

Laboratoires Servier provided funding to purchase actiwatches, but Servier had no role in the design of the protocol, or the acquisition, analysis and/or interpretation of data.

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